DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-152/S-026

Abbott Laboratories
Attention: Ms. Marilou Reed
Associate Director, Regulatory Affairs
100 Abbott Park Road
D-491, AP6B-1
Abbott Park, IL 60064-6108

28 SEP 2001

Dear Ms. Reed:

Please refer to your supplemental new drug application dated November 10, 1999, received November 12, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Isoptin SR (verapamil HCl) Tablets.

We acknowledge receipt of your submission dated July 30, 2001.

This supplemental new drug application provides for final printed labeling revised as follows:

The addition to the **PRECAUTIONS: Drug Interactions** section of the following:

> **Cytochrome inducers/inhibitors:** In vitro metabolic studies indicate that verapamil is metabolized by cytochrome P450 CYP3A4, CYP1A2, CYP2C8, CYP2C9 and CYP2C18. Clinically significant interactions have been reported with inhibitors of CYP3A4 (eg, erythromycin, ritonavir) causing elevation of plasma levels of verapamil while inducers of CYP3A4 (eg, rifampin) have caused a lowering of plasma levels of verapamil ; therefore, patients should be monitored for drug interactions.
>
> **Aspirin:** In a few reported cases, coadministration of verapamil with aspirin has led to increased bleeding times greater than observed with aspirin alone.
>
> **Grapefruit juice:** The intake of grapefruit juice may increase drug levels of verapamil.

Under **PRECAUTIONS: General**, the first sentence of the third paragraph of that subsection has been revised to include a precaution about worsening myasthenia gravis as follows:

> It has been reported that verapamil decreases neuromuscular transmission in patients with Duchenne's muscular dystrophy, prolongs recovery from the neuromuscular blocking agent vecuronium, and causes a worsening of myasthenia gravis.

The addition of "extrapyramidal symptoms" to the **ADVERSE REACTIONS** section under **Nervous System** is acceptable.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert included in your July 30, 2001 submission). Accordingly, the supplemental application is approved effective on the date of this letter.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact

John Guzman
Regulatory Health Project Manager
(301) 594-5312

Sincerely,

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research